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Definition

Urticaria consists of discrete areas of skin edema that are usually pruritic. *Angioedema,* which involves the deeper dermis and subcutaneous tissue, presents as localized areas of soft tissue swelling. Urticarial lesions are initially erythematous but often progress with central clearing to give a typical wheal and flare appearance. These lesions can vary from a few millimeters to several centimeters in diameter and may have serpiginous or polycyclic borders. Although most commonly involving the trunk and proximal extremities, the lesions can occur anywhere and are particularly common in areas of tight-fitting clothing. The lesions of angioedema are seldom pruritic but can produce an uncomfortable burning sensation and sometimes pain. Angioedema is most common in the loose tissues around the eyes and mouth. Urticaria and angioedema occur together in 49% of patients, urticaria is seen alone in 40%, and angioedema occurs alone in 11% of cases.

Urticaria is defined as chronic when lesions occur continuously or intermittently for longer than 6 weeks; although somewhat arbitrary, this definition of chronicity is clinically useful. Lesions of chronic urticaria usually last several hours and disappear in one area only to reappear in another.

Technique

A complete history and a physical examination are often necessary to identify the major etiologic categories of urticaria and angioedema. These are allergy, reactions to physical agents, familial disorders, and urticaria secondary to underlying disease. Acute urticaria, which may be part of generalized anaphylaxis, can often be attributed to a specific allergic exposure; this is seldom the case with chronic urticaria or angioedema. Allergens most frequently implicated in urticarial reactions include drugs, insect stings, and foods such as chocolate, eggs, nuts, and shellfish. Food additives such as food dyes and preservatives can also cause urticaria; metabisulfites used in restaurants as antioxidants in foods such as salads and fresh fruit have recently been reported to cause both urticaria and asthmatic reactions. Antibiotics, anticonvulsants, analgesics, and phenothiazines are drugs commonly identified. Skin testing to confirm IgE-mediated reactions to a limited number of drugs and biological agents such as penicillin, insulin, heterologous serum, and insect venom is sometimes useful. Urticaria resulting from substances inhaled or contacting the skin is rare but may be important in occupational exposures.

Physical urticaria from heat, cold, pressure, vibration, solar radiation, or exercise can usually be diagnosed from the patient's history. Cold-induced urticaria and solar urticaria are manifest by lesions on exposed areas. Cold-induced urticaria can result in life-threatening systemic reactions from swimming in cold water. Generalized heat urticaria, or cholinergic urticaria, produces characteristically small lesions 1 to 2 mm in diameter and occurs in situations causing cutaneous vasodilation such as exercise, hot baths, and emotional upsets. Dermatographia, which consists of urticaria occurring with skin stroking or scratching, is a common phenomenon that seldom produces severe symptoms. Urticaria or angioedema from vibration or sustained pressure is rare.

Hereditary angioedema is an autosomal dominant disorder characterized by episodes of angioedema without urticaria. In contrast to other types of chronic episodic angioedema, upper airway obstruction and abdominal pain are common features. The attacks of angioedema usually last 2 to 3 days. The interval between attacks is highly variable, ranging from weeks to months. Most patients with hereditary angioedema have low levels of the fourth component of complement (C4), even between attacks. A C4 level can be used as a screening test. If the level of C4 is low, the diagnosis should be confirmed by documenting low levels or decreased activity of C1 esterase inhibitor, the deficient enzyme in this disorder.

A large number of diseases have been reported in association with urticaria and angioedema including infections, connective tissue disorders, hyperthyroidism, and neoplastic disease. Most such associations are uncommon, however, and the underlying disorder is usually apparent after the history and physical examination. *Infections* associated with urticaria include helminthic infections, chronic sinusitis, dental abscess, and particularly type B hepatitis. Urticaria in hepatitis usually occurs as part of a prodrome associated with malaise, arthralgias, and sometimes arthritis and fever. The urticarial lesions frequently disappear as the patient becomes jaundiced.

Leukocytoclastic vasculitis, which is most often associated with palpable purpura, can also present as urticaria. Patients with urticarial vasculitis differ from those with primary idiopathic urticaria in having a higher prevalence of findings such as fever, arthralgias, and weight loss, as well as laboratory evidence of inflammation such as an elevated erythrocyte sedimentation rate. Individual urticarial lesions with underlying vasculitis often last more than 24 to 48 hours in duration and sometimes leave areas of skin discoloration. The most severely affected patients frequently have hypocomplementemia. The diagnosis can be confirmed by skin biopsy.

The cause of chronic urticaria and angioedema will elude detection in most patients. Most definable causes are apparent after a complete history and physical examination. Screening laboratory tests, such as a complete blood count, urinalysis, and an erythrocyte sedimentation rate, may be appropriate, but extensive laboratory studies, radiologic procedures, and allergy testing are seldom indicated.

Basic Science

Urticaria and angioedema are common patterns of reaction to a wide variety of stimuli acting through different mechanisms. The final common pathway is vasodilation, increased vascular permeability, and tissue edema. Immediate hypersensitivity involving the binding of IgE molecules to receptors on tissue mast cells is responsible for true allergic reactions. Mast cells are present in the skin in concentrations up to 7000 cells per cubic millimeter and are found in proximity to blood vessels. When complexes form between antigens (allergens) and IgE on mast cells surfaces, a series of biochemical reactions occurs, releasing vasoactive mediators such as histamine from mast cell granules or metabolites of arachidonic acid from membrane phospholipids. Important products of arachidonic acid metabolism include the prostaglandins and leukotrienes. IgE-mediated reactions have also been implicated in some types of physical urticaria, including cold urticaria and dermatographia.

Urticaria is also seen in diseases with circulating immune complexes, such as systemic lupus erythematosus and type B hepatitis. The immune complexes activate the complement cascade, generating C3a and C5a, potent anaphylotoxins capable of causing the release of histamine and other mediators from mast cells. Histamine can also be released directly from mast cells by the pharmacologic action of drugs such as opiate derivatives. A mediator-releasing action independent of IgE has also been demonstrated for radiographic contrast media and extracts of some foods, including eggs, strawberries, and shellfish.

Hereditary angioedema is associated with a deficiency of C1 esterase inhibitor, a serum protein that not only inhibits the activated first component of complement but also blocks the fibrinolytic enzyme plasmin, activated Hageman factor, and kallikrein. Minor trauma, which can activate Hageman factor, often precipitates attacks. Activation of Hageman factor may be the initiating event leading to the generation of vasoactive substances from a complex interaction of the coagulation, fibrinolytic, kinin, and complement systems.

For most cases of chronic urticaria and angioedema, the etiology and pathogenic mechanisms remain unknown. In some entities, such as cholinergic urticaria, the pathogenic mechanism is unknown even though the inciting stimulus may be clearly defined.

Clinical Significance

Urticaria and angioedema are common conditions with a cumulative incidence of 10 to 15% of the general population. For most individuals, the episodes are brief and self-limited and are probably the result of allergen exposure. Because acute urticaria or angioedema can be part of a generalized anaphylactic reaction, patients who develop either one shortly after drug administration or an insect sting should be observed until improvement is seen. Chronic, persistent urticaria can occasionally be a clue to an important underlying disorder. In contrast to acute lesions, however, the etiology of chronic urticaria and angioedema usually remains unknown. Most patients with chronic idiopathic urticaria and angioedema will have a remission of their disease within 6 months; in some individuals the disease may persist continuously or intermittently for years.

Recognizing the signs and symptoms of hereditary angioedema is important because the disease can cause fatal airway obstruction, and effective prophylactic treatment is available.

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